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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/319,411	10/06/1994	PETER NIELSEN	ISIS1158	8648

7590 11/20/2002

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EXAMINER	
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ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
08/319,411	Nielsen et al.
Examiner	Art Unit
Ardin Marschel	1631

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jul 22, 2002

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1, 5, 8-10, 12, 13, 15, 20, 22-24, 30-32, 37, and 39-52 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1, 5, 8-10, 12, 13, 15, 20, 22-24, 30-32, 37, and 39-52 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☒ The proposed drawing correction filed on Jul 17, 2002 is: a) ☐ approved b) ☒ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 08/108,591 .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

In view of the appeal brief, filed 7/22/02, and newly found rejections summarized herein, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below. This reopening of prosecution is based primarily on an incomplete analysis of the benefit that should or should not be accorded to the prior application, U.S. Serial Number 08/108,591; now U.S. Patent 6,395,474; as well as other newly applied rejections as summarized below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

file a reply under 37 CFR 1.111; or

request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131, or 1.132) or other evidence are permitted. See 37 CFR 1.93(b)(2).

Applicants' arguments, filed 7/22/02, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

DRAWING INFORMALITIES REMAIN UNCORRECTED:

Applicant is hereby notified that the required timing for

the correction of drawings has changed. See the last 6 lines on the sheet which is attached entitled "Attachment for PTO-948 (Rev. 03/01 or earlier)". It is noted that a PTO Form 948 was mailed with Paper No. 46 on 6/18/02 with an Attachment for PTO-948. It is also noted that a drawing correction, filed 7/17/02, was indicated on the Advisory Action, mailed 10/9/02, as being on different sized paper compared to the other drawings and thus non-acceptable. Due to the above notification Applicant is required to submit drawing corrections within the time period set for responding to this Office action. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office action.

LACK OF SCOPE OF ENABLEMENT:

Claims 1 and 5 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the PNA conjugate molecules wherein the backbone structures are those cited specifically by detailed chemical structures in instant claims 30, 37, and 39-50; does not reasonably provide enablement for broader and more generic PNA structures as claimed in instant claim 1, for example. Only the name "peptide nucleic acid plus the characterization of having a backbone" with at least "an amino end", a "carboxyl end", and a "plurality of amino groups" are cited in said claim 1 regarding the PNA chemical backbone structure which includes a multitude of potential

chemical structures. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

It is noted that the instant specification lacks a clear and concise definition of PNA conjugate structure as described in a rejection below under 35 U.S.C. § 112, second paragraph, thus resulting in a reasonable interpretation being that PNA structure

in the instant disclosure may include very broad and generic structures. A generic, but unclear as to metes and bounds, structural description is included in the specification on page 3, lines 1-6, and in the instant claims with structures, such as set forth in claims 30 etc. No specific PNA conjugate backbone statement has been found that limits the backbone other than as noted in said page 3 citation or in either instant claim 1 or structures as in claim 30. Consideration of the numerous Examples of synthetic procedures starting in the specification on page 46, line 35, reveals that PNA structural synthetic procedures regarding the important central portion of said structure; that is, being the backbone; starts with Example 2 on page 47 with a monomer of 2-aminoethyl glycine with other structures described as to preparatory methods such as 2-aminoethyl serine types and diaminopropinate type backbones which reasonably may be extrapolated to other diamino-alkyl backbone structures. Further consideration of Examples 2 through the final Example 122 on pages 47-170 has failed to reveal synthetic description of other backbone chemical structural types. It is also noted that each step and intermediate synthesis in the PNA conjugate syntheses on said pages 47-170 is complex and detailed in nature and must include the usage of many protecting groups for reactive sites so as to properly direct synthetic steps to desired sites only, with subsequent deprotection. Also, any

completed PNA conjugate molecule(s) require(s) several of these complex synthetic steps. Thus specific guidance regarding PNA conjugate backbone structures is limited as filed to those of the 2-aminoethyl glycine etc. structures as listed above. Instant claims 1 and 5 are not limited as worded to such a backbone structure. Such multi-step complex synthetic methods with complex protection/deprotection schemes are deemed to require specific guidance for synthesis of a claimed compound. Without such specific guidance such multi-step etc. syntheses require undue experimentation, especially for PNA structures with unlimited backbone content such as apparently included within instant claims 1 and 5.

VAGUENESS AND INDEFINITENESS:

Claims 1, 5, 8-10, 12, 13, 15, 20, 22-24, 30-32, 37, and 39-52 are rejected, as discussed below, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of what applicants intend as a peptide nucleic acid and relatedly what constitutes a peptide nucleic acid conjugate. It is noted that the instant specification at page 3, lines 1-4, defines peptide nucleic acids as having an oligonucleotide backbone which has been replaced with a backbone having peptide linkages. In lines 3-4, "each" subunit is

characterized as having an attached "naturally occurring or non-naturally occurring base". No other structural limitations are set forth in this page 3 definition. Then chemical structures are set forth as peptide nucleic acid conjugates starting in the specification on page 7, line 21, wherein moieties "L" and "L_m" are optionally hydrogen, hydroxy, etc. as cited in the bridging paragraph between pages 7 and 8 which includes naturally and non-naturally occurring nucleobases, but also non-nucleobase options. It seems reasonable to expect that a peptide nucleic acid conjugate contains within it at least one peptide nucleic acid portion and at least one conjugate portion. Claims 1 and 5 require a backbone with an amino end, a carboxyl end, a plurality of amino groups each with a tethered nucleobase, and a conjugate attached to at least one amino or carboxyl end. This is yet another definition of a peptide nucleic acid conjugate. L moieties are also present within peptide nucleic acid conjugates as required in pending claims starting with claim 8, which depends from claim 37 having said L type moieties. As worded, these claims, such as claim 37, include chemical structures wherein none of the L moieties are a nucleobase. It is noted in claim 37 that the L moiety contains R^{12} which optionally may or may not be a nucleobase due to one option for R^{12} being a DNA intercalator. What is meant by claiming peptide nucleic acid conjugate structures wherein there is no nucleic acid or

nucleobase type moiety therein? In such structures, what is meant as the peptide nucleic acid portion? These definitions for peptide nucleic acid also conflict in that the page 3 definition requires a base at each subunit whereas the page 7-8 structure or claims 37 etc. lack such a requirement and may have a DNA intercalator, hydrogen, hydroxy, etc. at each subunit, rather than a nucleobase. Clarification via clearer claim wording as the metes and bounds of what is meant by a peptide nucleic acid conjugate is requested regarding the L moiety limitations therein.

Connected and related to the above paragraph which indicates unclarity as to the metes and bounds of what applicants intend for a peptide nucleic acid conjugate, is unclarity as to what conjugate practice is meant also. As noted above various peptide nucleic acid conjugates are claimed without a nucleobase requirement. This may be reasonably interpreted that there is no nucleobase requirement for what is meant regarding the peptide nucleic acid portion of a peptide nucleic acid conjugate. It is also noted that the definition of a conjugate in the specification on page 15, lines 14-24, include several conjugate options which broadly include a nucleobase structure. For example, a nucleobase is aromatic and lipophilic. A nucleobase is also a reporter molecule due to the well known UV absorbance character of nucleobases which is commonly utilized in the art to

detect nucleic acids via the UV light absorbance at an approximately 260 nanometer wavelength. Also crosslinking to nucleobases is well known thus also including nucleobases as a type of crosslinking agent conjugate. For example, thymine dimers are examples of such crosslinking agent usage for nucleobases. If the peptide nucleic acid portion of a peptide nucleic acid conjugate may lack any nucleobase and a conjugate portion may be a nucleobase, then a peptide nucleic acid which contains a backbone, amino and carboxy termini, and nucleobases also meet the requirements of being a peptide nucleic acid conjugate. If so, what is meant by claims containing the phrase "peptide nucleic acid conjugate" when the metes and bounds of what is meant by a "peptide nucleic acid conjugate" and a "peptide nucleic acid" are vague and indefinite. The above unclarities also leads to unclear options as to what peptide nucleic acid conjugate practice may meet the claim limitations. For example, if a peptide nucleic acid contains what is normally 20 monomeric units, this may be reasonably characterized as being a 19 monomer length peptide nucleic acid with a nucleobase containing conjugate attached at the end which is initially the 20th monomer, but may also be referred to as a conjugate due to the broad definition of what a conjugate is as discussed above. Clarification via clearer claim wording is requested.

Another unclarity in the claims is that the page 3, lines 1-

4, definition of a peptide nucleic acid is that an oligonucleotide backbone is replaced with a peptide linkage containing backbone which indicates that the peptide nucleic acid is at least an oligomer type of molecule. This conflicts with presently pending claims 42-46 and 50 which are not oligomeric type molecules but rather monomers but yet called "peptide nucleic acid" conjugates. Clarification via clearer claim wording is requested.

Claims 1 and 5 are additionally vague and indefinite as to what is meant regarding the attachment of a tethered nucleobase to amino groups. It is noted that claims 1 and 5 require that the backbone contains an amino end, a carboxyl end, and a plurality of amino groups. It is noted that said amino end reasonably contains an amino group. Both of claims 1 and 5 then require that "said amino groups" each has a "tethered nucleobase". As worded, a tethered nucleobase apparently is required at the amino end as well as at any other amino groups. Alternatively, the requirement for a tethered nucleobase to only internal or non-end amino groups may be what applicants intend. The claim wording, however, does not clearly distinguish between these two confusing alternatives. Clarification via clearer claim wording is requested.

Regarding the instant claims which cite specific chemical structures, the cooperativity or linkages between the various

moieties therein is vague and indefinite. In claim 37; for example; moieties "A" and "A_m" have undefined linkage practice. The "A" and "A_m" moieties, as depicted in the claims as structures IIa - IId, lack any definition as to which side links to the backbone of the peptide nucleic acid conjugate versus the "L" or "L_m" moiety. Clarification via clearer claim wording is requested.

PRIORITY CLAIM AS TO BENEFIT OF THE DISCLOSURE OF 08/108,591:

The instant invention is directed to various peptide nucleic acid conjugates wherein a peptide nucleic acid is conjugated to a conjugate moiety. In these instantly defined peptide nucleic acid conjugates the attachment sites for such conjugate moieties onto the peptide nucleic acid basic structure include the termini; the backbone; the tether to a ligand(s), denoted "L" in certain structures as instantly claimed; and the ligand(s), L, it or themselves. The term "conjugate" is defined, in the instant specification on page 15, lines 14-24, to include a wide variety of conjugate moiety types. A reconsideration of the disclosure of priority document Serial Number 08/108,591; now U.S. Patent No. 6,395,474 (herein referred to as "Buchardt '474") reveals that numerous specific PNA structures are therein disclosed but not conjugate options as broadly listed as in the instant application. For ease of citation, this discussion of 08/108,591 will utilize column and line numbers from the Patent No.

6,395,474; which has issued from application serial number 08/108,591; and thus will be referred to as "Buchardt '474". Specific PNA conjugates only, however, are disclosed in Buchardt '474 such as a terminal reporter in Figure 5 and various "L" moieties which fall into conjugate characterization as listed in column 4, line 66, through column 5, line 7. The tether for the "L" moiety in the PNAs of Buchardt '474 and the backbone is limited to R groups listed as R^1 - R^7 and $R^{7'}$ which are very limited as to what conjugate type of moiety that these might be. These R groups are mostly hydrogen, hydroxy, or alkyl groups with some being amines or thio containing moieties and side chains of naturally occurring alpha amino acids. A number of terminal R groups are listed in column 5, lines 58-65, which overlap with several of the instant conjugate types. It is noted that Buchardt '474 lacks any discussion of L moieties, such as a nucleobase, further attached with a conjugate moiety. Some generic conjugation practice is cited in Buchardt '474 in column 10, lines 20-47, but without defining the site of attachment to the PNA basic structure and thus this section of Buchardt '474 fails to provide any further benefit for embodiments which do define specific attachment site(s). The above summary appears to completely list the conjugate practice disclosed in said Buchardt '474. Thus, the above conjugate structure disclosures only, and not more, are granted benefit to at least the effective filing

date of Buchardt '474 which is at least the 102(e) date of Nov. 22, 1993. The earlier priority documents listed in the instant application as PCT/EP92/01219, DK 986/91, DK 987/91, and DK 510/92 have also been reviewed and do not extend the subject matter benefit to cover more than what has been summarized above as to peptide nucleic acid conjugates over that of Buchardt '474, albeit providing benefit earlier dates for certain embodiments therein.

PRIOR ART BASED REJECTIONS:

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 5, 8-10, 15, 20, 22-24, 30-32, 37, 40, 42, 45, and

50 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shah et al.(P/N 5,705,333).

This rejection is maintained and reiterated from the previous office action, mailed 8/29/01, but modified and expanded as explained as follows. Applicants argue that Shah et al. is not prior art due to the priority document; serial number 08/108,591 (now Buchardt '474); predating the Shah et al. filing date and that said priority document discloses the embodiments in Shah et al. which form the basis for this rejection. Consideration of said priority document and parent priority documents has revealed only limited disclosures which supply benefit to at least 11/22/93 as summarized in the above priority claim analysis. The description of a number of PNA conjugates in Shah et al., however, are outside of said limited disclosures and therefore are not predated by 08/108,591.

As discussed above, one of the conjugate types which was not disclosed in Buchardt '474 etc. was that of a conjugate moiety specifically further attached onto a nucleobase type L moiety within the PNA conjugate structure. It is also noted that the generic conjugate discussion in Buchardt '474 at column 10, lines 20-47, lacks any mention of a crosslinking moiety even generically attached to a PNA basic structure. Shah et al. discloses PNA structures as depicted in Figures 4A - 8 wherein the component "Nu" therein corresponds to moiety "L" as instantly

described. In Shah et al. this "Nu" component may be a nucleobase or analog thereof. Shah et al. in column 10, line 12, through column 11, line 8, lists a number of specific nucleobase analogs. One specific type of nucleobase analog is that modified by a crosslinking agent as noted in column 10, lines 43-49, in Shah et al. The lack of benefit to the above discussed priority document for this type of PNA conjugate structure supports this rejection based on these embodiments in Shah et al.

Another type of conjugate practice which is described in Shah et al. and not in said priority documents are certain terminally attached conjugates. Shah et al. describes the conjugating of carrier molecules in column 17, lines 37-55. Certain such carrier molecule conjugates which are not found in said priority documents are those listed as fluorescent dyes, crosslinking agents (Some specific crosslinkers are set forth in column 19, lines 31-45.), alkylating agents (Some specific alkylators are set forth in column 19, lines 51-57.), chain cleaving agents (Some specific cleaving agents are set forth in column 19, line 58, through column 20, line 13.), specific proteins such as peroxidases, IgG, alkaline phosphatases, and nucleases. It is noted that Buchardt '474 at column 5, line 63, cites reporter ligands as terminal PNA conjugates. The presence of the word "ligand" in the phrase "reporter ligand" is reasonably understood to indicate that some type of binding

characteristic therein corresponds to the ligand characteristic as normally defined in the art. Thus, a reporter ligand as in Buchardt '474 is reasonably distinct from a fluorescent dye as described in said Shah et al. list of conjugates as such dyes are generally not characterized as being any type of binding "ligand". Other conjugates are listed in Shah et al. in column 17, line 55, through column 18, line 13, as long chain fatty triglyceryl residues, cytokines, and polycyanoacrylates. The practice of acridine derivatation terminal group is also cited in Shah et al. in column 19, lines 12-14. None of these specific conjugate groups are disclosed in Buchardt '474 or related priority documents and thus are not predated by said priority documents.

Shah et al. motivates and describes the attachment sites for modifying groups as at "virtually any position" in column 20, lines 14-17, followed by guidance as to not preventing hydrogen bonding between a PENAM and its target nucleic acid. Specific conjugate practice has been summarized above in Shah et al. which is not predated by priority documents for the instant application thus supporting this rejection for these conjugate constructs.

It has been previously summarized in previous office actions that the PENAMs of Shah et al. clearly include PNA structures as instantly claimed. It is additionally noted that syntheses of conjugates including the basic PNA structure is cited at several

locations within Shah et al. The basic structures of Shah et al. are summarized in columns 3-12 which is inclusive of moiety "E" being Carbon or Nitrogen as in the instantly claimed PNAs. The spacer groups, S1 - S3, of Shah et al. are listed in column 8, lines 33-61, which are also those of the instantly claimed PNA conjugates and at least include $-CH_2-$ lengths of 2-6 etc. as noted specifically in column 8, lines 57-61. These correspond to specific "y" and "z" parameters in the instant claims. Synthetic details for PENAMs are set forth in column 16, line 64, through column 17, line 36, which is also that of PNA conjugates via the basic peptide synthesis methodology being applied to analogs of amino acids as further detailed in Shah et al. in column 27, line 1, through column 35, line 10. These synthetic instructions combined with the above described specific conjugate attachment sites suggests and motivates species of PNA conjugates as are instantly claimed. Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to prepare PNA conjugates of Shah et al. which are motivated and suggested therein to result in species of the instant invention.

Claim 1 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Lobberding et al.(P/N 5,623,049).

This rejection is maintained and reiterated from the previous office action, mailed 8/29/01. Applicants also argue this rejection regarding the priority document 08/108,591. This

argument is also non-persuasive here in that the Lobberding et al. conjugates also include terminal conjugate groups which are not predated by 08/108,591. One such terminal conjugate group is that of a cell recognition agent as described in the reference in column 5, line 38, through column 6, line 4, as a carrier system. It is noted that terminal conjugates are listed in Buchardt '474 in column 5, lines 60-65, but do not contain listing of cell recognition or receptor units as also instantly claimed for terminal conjugates. Applicants further argue that the reference does not suggest the species of PNA conjugate structure as instantly claimed. In response the structure described in column 2, lines 1-58, clearly suggests species of compounds as instantly claimed. Moieties "M" and/or "L" are the above discussed carrier systems or hydrogen as instantly claimed. Moieties "G" and "A" are methylene chains of lengths 2-5 methylenes. Moieties "E" and "K" are similarly methylene chains of 2-5 methylenes as are also in the instantly claimed PNA backbones. The tether to the base "B" of the reference may be another methylene chain as instantly claimed or with a carbonyl as the "D" moiety also an option as instantly claimed. "B" is either a nucleobase or analogs thereof as also instantly claimed. The oligomeric structure of the compounds of the reference is shown by parameter "s" being 1-30 as also embodiments of the instant PNA conjugate molecules. It is noted that the synthetic methodology in Lobberding et al. is

limited to the preferred embodiments of PNA basic structure as depicted in column 6, lines 16-55, which is thus enabling only for embodiments of the instant claims wherein generic backbones are cited with nitrogen linkages to the tethered nucleobase. Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the preferred embodiments therein with carrier systems being conjugated at their termini with cell receptor or recognition units thus resulting in the practice of species of the instantly claimed invention.

OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS:

The following double patenting rejections are reiterated and maintained from the previous office action, mailed 8/29/01.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 5, 8-10, 12, 13, 15, 20, 22-24, 30-33, 37, 39-43, and 45-52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 5,539,082; itself, or, alternatively, in view of any one of Saito et al., Fink et al., or Leon et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

Upon reconsideration of the metes and bounds of PNA conjugates as instantly claimed, it is noted that one of the above discussed issues under 35 U.S.C. § 112, second paragraph, is unclarity as to what is meant regarding the metes and bounds of PNA conjugates. On interpretation that was set forth is that a nucleobase is a conjugate as instantly defined. Thus, a PNA with a terminally attached last nucleobase monomer in a PNA may be interpreted as a PNA conjugate as instantly defined. Thus, the claimed subject matter of claims 1 and 2 of P/N 5,539,082 are within the metes and bounds of instantly claimed terminally conjugated PNA conjugates. The PNA structures of claims 1 and 2 of P/N 5,539,082 as summarized below are within the instantly claimed PNAs with either N-terminal or C-terminal monomer being a conjugate as instantly defined results in common embodiments with the instant claims 22, 40, 42, and 50.

In the alternative, the Lysine containing compounds, either at a terminus or as $R^{7'}$ of claims 1-3 of P/N 5,539,082 are PNA conjugates in view of any one of Saito et al., Fink et al., or Leon et al. Applicants have argued that there is no evidence of record that lysine is a crosslinking agent. Saito et al., Fink et al., and Leon et al. are references which well document the usage of Lysine as an agent in crosslinking thus documenting this characteristic of Lysine in claims 1-3 of P/N 5,539,082. The remainder of this rejection is repeated as follows from the previous office action, mailed 8/29/01, but adding the note that Lysine is also in the backbone at the $R^{7'}$ residue as a normal sidechain of the amino acid, lysine which participates in crosslinking reactions. Claims 1 and 2 of the Patent include PNAs with lysine at one terminus and claims 1-3 all have the backbone lysine as an optional amino acid side chain. It is well known that Lysine is a crosslinking agent in various biomolecules, such as protein as a result of its amino side chain as further documented by Saito et al, Fink et al, and Leon et al. This is also an embodiment of instant claims 1, 40, and 50, for example, wherein a crosslinking agent at a terminus of a PNA is a specie therein. If a terminal nucleobase containing PNA moiety is the tethered nucleobase and the penultimate PNA monomer moiety contains a nucleobase this is within the definition of a conjugate which is a "reporter molecule" as given in instant

claim 5. Such PNAs are also species of claims 1 and 2 of the Patent. Instant claims 30-33 require either an L or R3 to be a conjugate. It is noted that a conjugate includes a reporter molecule which includes a nucleobase which is well known, as well as commonly utilized, for UV detectability. Similarly, instant claims 37 and 39 includes such species as described above with more specific PNA chemical structure thus also supporting this rejection over the Patent. It is noted that instant claims 39 and 49 require an R group on the linkage to the nucleobase to be a conjugate. Such R groups are given in the Patent in that alkylthio or amino groups are present as options which are well known crosslinking agent sites. Instant claims 41, 47, and 48 require a conjugate at certain R groups which includes linkages in the backbone of the PNA. Such conjugates may be crosslinking agents as in an amino acid side chain such as lysine which is a side chain embodiment given as $R^{7'}$ in claims 1 and 2 of the Patent thus documenting a common embodiment. Instant claims 42 and 43 are directed to a monomer as is claim 3 of the Patent wherein at least the R group or some group on the nucleobase attachment must be a conjugate which includes crosslinking agents such as alkylthio or amino moieties which are also options in the nucleobase attachments of the Patent claim 3. Instant claims 45 and 46 require a conjugate on the C or D groups which has been noted above as being a specie of the Patent claims via the

options of amino acid side chains being at said $R^{7'}$.

Claims 1, 5, 8-10, 12, 13, 15, 20, 22-24, 30-33, 37, 39-43, and 45-52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,773,571; itself, or, alternatively, in view of any one of Saito et al., Fink et al., or Leon et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

Equivalent reasoning to base this rejection on is reiterated here from the above reasoning regarding P/N 5,539,082 regarding Lysine being a crosslinking agent.

Claims 20, 22, 43, and 45-48 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1, 5, and 8 of U.S. Patent No. 5,786,461; in view of any one of Saito et al., Fink et al., or Leon et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

Equivalent reasoning to base this rejection on is reiterated here from the above reasoning regarding P/N 5,539,082 regarding Lysine being a crosslinking agent as one option for $R^{7'}$ as a

Lysine amino acid side chain.

Claims 1, 5, 8-10, 12, 13, 15, 20, 22-24, 30-33, 37, 39-43, and 45-52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,773,571; itself, or, alternatively, in view of any one of Saito et al., Fink et al., or Leon et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

Equivalent reasoning to base this rejection on is reiterated here from the above reasoning regarding P/N 5,539,082.

Claims 1, 8-10, 15, 20, 22-24, 30-32, 37, 40, 48, 50, and 51 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 9 of U.S. Patent No. 5,719,262; itself, or, alternatively, in view of any one of Saito et al., Fink et al., or Leon et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

Equivalent reasoning to base this rejection on is reiterated here from the above reasoning regarding P/N 5,539,082 regarding Lysine being a crosslinking agent.

Claims 1, 8-10, 15, 20, 22-24, 30-32, 37, 40, 48, 50, and 51 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4, 5, and 7 of U.S. Patent No. 6,395,474; itself, or, alternatively, in view of any one of Saito et al., Fink et al., or Leon et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

Equivalent reasoning to base this rejection on is reiterated here from the above reasoning regarding P/N 5,539,082 regarding Lysine being a crosslinking agent.

Claims 22-24, 45, 46, and 50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8, 34, 35, 37, 40-47, 49-51, 53-56, 61-63, 66-69, 71-76, and 89-93 of copending application Serial No. 08/468,719. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims. For example, claim 49 of the copending application include PNAs with various side chains off the backbone, which include alkylthio or amino side chains which are well known to be crosslinking agents, as well as a reporter molecule as an L group. A reporter molecule

is instantly included as a conjugate. Instant claims 22-24, 45, 46, and 50 includes reporter molecules as the L group in the basic PNA structures as well as backbone conjugate moieties as noted above which therefore includes the structure of claim 49 of the copending application. The remaining claims of the copending application are included herewith due to their being limited to basic normal PNA components which are also those of the instant claim. This rejection is maintained as not being argued in the Appeal Brief, filed 7/22/02.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 8-10, 15, 20, 37, 40, 50, and 51 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent Serial No. 6,414,112; taken in view of Summerton et al.(WO 86/05518); taken further in view of Saito et al., Fink et al., or Leon et al. regarding Lysine as being a crosslinking agent. See above discussion regarding this crosslinking character in the cited reference. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims. For example, claim 1 of said Patent include PNAs with Lysine at one terminus, but

requiring one 2,6-diaminopurine as an L group. It is well known that Lysine is a crosslinking agent, such as when present in peptides or proteins. This is also an embodiment of instant claims 1 and 40, for example, wherein a crosslinking agent at a terminus of a PNA is a specie therein. The substitution of a 2,6-diaminopurine nucleobase for other nucleobases, such as in the instant claims, is lacking in 6,414,112 but Summerton et al. clearly describe the equivalence of such nucleobases in the abstract and the document as a whole. Such functional equivalents are deemed thus suggested and motivated thereby for documenting the common embodiments between the instant claims and that of 6,414,112. Summerton et al. (WO 86/05518) motivates and suggests that nucleobases for PNAs include 2,6-diaminopurine on page 20, line 30, through page 21, line 7, and specifically motivates such a base type for stronger base pair bonding for adjusting PNA affinity on page 48, lines 1-22, if desired. Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to substitute such nucleobases for natural nucleobases within the PNA oligomer practice of the instant application; thus resulting in the practice of the claims of the instant application. A specific motivation for stronger base pair bonding is hereby pointed to on page 48 of Summerton et al.(WO 86/05518), as desired for PNA design.

Claims 1, 8-10, 15, 20, 22-24, 37, 40, 48, 50, and 51 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26 and 28 of copending application Serial No. 09/106,667; taken further in view of Saito et al., Fink et al., or Leon et al. regarding Lysine as being a crosslinking agent. See above discussion regarding this crosslinking character in the cited reference. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims. For example, claim 28 of the copending application include PNAs with various side chains off the backbone, which include alkylthio or amino side chains which are well known to be crosslinking agents, as well as a reporter molecule as an L group. A reporter molecule is instantly included as a conjugate. The instant claims includes reporter molecules as the L group in the basic PNA structures as well as backbone conjugate moieties as noted above which therefore includes the structure of claim 28 of the copending application. The remaining claims of the copending application are included herewith due to their being limited to basic normal PNA components which are also those of the instant claim.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been

patented.

Claims 1, 5, 8-10, 12, 13, 15, 20, 22-24, 30-32, 37, and 39-52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-20, 22, 23, and 25-37 of copending application Serial No. 08/817,067; itself, or, alternatively, taken further in view of Saito et al., Fink et al., or Leon et al. regarding Lysine as being a crosslinking agent. See above discussion regarding this crosslinking character in the cited reference. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 8-10, 15, 20, 37, 40, 50, and 51 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 13, 14, 15, 21, and 22 of copending application Serial No. 09/337,304; taken in view of Summerton et al.(WO 86/05518); taken further in view of Saito et al., Fink et al., or Leon et al. regarding Lysine as being a crosslinking agent. See above discussion regarding this crosslinking character in the cited

reference. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims. For example, claim 1 of said application includes PNAs with Lysine at one terminus, but requiring one 2,6-diaminopurine as an L group. It is well known that Lysine is a crosslinking agent, such as when present in peptides or proteins. This is also an embodiment of instant claims 1 and 40, for example, wherein a crosslinking agent at a terminus of a PNA is a specie therein. The substitution of a 2,6-diaminopurine nucleobase for other nucleobases, such as in the instant claims, is lacking in 09/337,304; but Summerton et al. clearly describe the equivalence of such nucleobases in the abstract and the document as a whole. Such functional equivalents are deemed thus suggested and motivated thereby for documenting the common embodiments between the instant claims and that of 09/337,304. Summerton et al. (WO 86/05518) motivates and suggests that nucleobases for PNAs include 2,6-diaminopurine on page 20, line 30, through page 21, line 7, and specifically motivates such a base type for stronger base pair bonding for adjusting PNA affinity on page 48, lines 1-22, if desired. Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to substitute such nucleobases for natural nucleobases within the PNA oligomer practice of the

instant application; thus resulting in the practice of the claims of the copending application. A specific motivation for stronger base pair bonding is hereby pointed to on page 48 of Summerton et al.(WO 86/05518), as desired for PNA design.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 8-10, 15, 20, 37, 40, 50, and 51 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2, 13-15, and 24 of copending application Serial No. 09/230,088; taken in view of Summerton et al.(WO 86/05518); taken further in view of Saito et al., Fink et al., or Leon et al. regarding Lysine as being a crosslinking agent. See above discussion regarding this crosslinking character in the cited reference. Although the conflicting claims are not identical, they are not patentably distinct from each other because various embodiments in each set of claims are common embodiments between said sets of claims. For example, claim 1 of said application includes PNAs with Lysine at one terminus, but requiring one 2,6-diaminopurine as an L group. It is well known that Lysine is a crosslinking agent, such as when present in peptides or proteins. This is also an embodiment of instant claims 1 and 40, for example, wherein a crosslinking agent at a terminus of a PNA is a specie therein.

The substitution of a 2,6-diaminopurine nucleobase for other nucleobases, such as in the instant claims, is lacking in 09/337,304; but Summerton et al. clearly describe the equivalence of such nucleobases in the abstract and the document as a whole. Such functional equivalents are deemed thus suggested and motivated thereby for documenting the common embodiments between the instant claims and that of 09/337,304. Summerton et al. (WO 86/05518) motivates and suggests that nucleobases for PNAs include 2,6-diaminopurine on page 20, line 30, through page 21, line 7, and specifically motivates such a base type for stronger base pair bonding for adjusting PNA affinity on page 48, lines 1-22, if desired. Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to substitute such nucleobases for natural nucleobases within the PNA oligomer practice of the instant application; thus resulting in the practice of the claims of the copending application. A specific motivation for stronger base pair bonding is hereby pointed to on page 48 of Summerton et al.(WO 86/05518), as desired for PNA design.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

SPECIFICATION INFORMALITIES:

The disclosure is objected to because of the following informalities:

In the specification on page 7, line 18, the word "prefereably" appears to be misspelled.

In the specification on page 7, line 23, the word "ineteger" appears to be misspelled.

In the specification on page 13, line 32, the word "deravative" appears to be misspelled.

In the specification on page 19, line 14, the word "derivitization" appears to be misspelled.

In the specification on page 20, line 21, the word "ot" appears to be misspelled.

In the specification on page 41, line 31, the word "redily" appears to be misspelled.

In the specification on page 41, line 32, the word "from" is confusingly repeated.

In the specification on page 43, line 37, the word "donot" appears to be confusingly runtogether.

In the specification on page 43, line 37, the word "posses" appears to be misspelled.

In the specification on page 59, line 1, the word "dublets" appears to be misspelled.

In the specification on page 60, line 9, the word "mmHg"

appears to be two words runtogether.

In the specification on page 70, line 10, the temperature "0oC" appears to contain a incorrectly non-superscripted "o" or degree designation.

In the specification on page 74, line 12, the word "comound" appears to be misspelled.

In the specification on page 75, line 25, the word "comound" appears to be misspelled.

In the specification on page 79, line 27, the word "Sodiumtriacetoxyborohydride" appears to be confusingly two words that are runtogether.

In the specification on page 93, line 15, the word "tretment" appears to be misspelled.

In the specification on page 104, line 33, the word "complimentary" appears to be misspelled in context.

In the specification on page 136, line 17, the word "quantative" appears to be misspelled.

In the specification on page 155, line 16, the word "targed" appears to be misspelled.

From the above partial listing of misspellings etc., it is apparent that numerous such informalities exist in the instant specification. Applicants are requested to review the specification in its entirety in order to identify these informalities and amend as appropriate.

REQUIREMENT FOR A SUBSTITUTE SPECIFICATION:

A substitute specification is required because of the numerous informality corrections needed therein as at least partially summarized above. The substitute specification filed must be accompanied by a statement that it contains no new matter. Such statement must be a verified statement if made by a person not registered to practice before the Office.

CLAIM INFORMALITIES:

Another informality is present in claims 48 and 49 in that the superscripting of R3 is inconsistent in the respective paragraphs near the end of these claims which define the conjugate practice of L and R3.

Appropriate correction is required.

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703)308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703)308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703)308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (703)305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

ARDIN H. MARSCHEL
PRIMARY EXAMINER

November 19, 2002